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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,223	03/09/2001	Robert Korngold	KOR01-NP002	6791

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	10

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/803,223	Korngold et al.
Examiner	**Art Unit**
G.R. Ewoldt	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 28, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2, 3, and 5-11* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2, 3, and 5-11* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's amendment and remarks, drawings, and declaration filed 1/28/03, are acknowledged.

2. Applicant's new drawings have been found acceptable by the Examiner.

3. It is noted that the new declaration has not been dated by Inventor Flomenberg. However, MPEP 602.05 states that a new declaration will no longer be required in instances wherein the date of execution has been omitted. Accordingly, the declaration has been found acceptable.

4. Claims 2, 3, and 5-11 are pending and being acted upon.

5. In view of Applicant's amendments, all previous objections to the claims and rejections of claims under the second paragraph of 35 U.S.C. 112 have been withdrawn.

6. Applicant has traversed the denial of the benefit of priority to U.S. Provisional Application No. 60/188,391. Specifically, Applicant argues that the terms inhibiting and preventing are interchangeable because "inhibit" has been defined as "to retard or prevent". Applicant further argues that the '391 application does actually teaches the separation step of Claim 5 at page 2.

Regarding the interchangeability of the terms inhibit and prevent, Applicants argument that inhibit can be defined as retard *or* prevent demonstrates that the term "inhibit" is broader than the term "prevent". Thus, the instant claims encompasses a broader method than that which is disclosed in the provisional application. Accordingly, the denial of priority is proper.

Regarding the teaching of the separation step of Claim 5, Applicant is advised that the disclosure at page 2 of the '391 application indicates a separation step involving PBMC whereas Claim 5 recites a step involving hematopoietic stem cells. Thus, the fractions of $CD34^+$ and $CD34^-$ cells of the '391 application are not the same as the cell fractions of the instant claims. Accordingly, the denial of priority is again proper.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 3 and 5, and newly amended Claim 2, and newly added Claims 6-11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenfeld et al. (1995, IDS) in view of Small et al. (1999, IDS) and U.S. Patent No. 5,668,112 (1997, IDS).

Rosenfeld et al. teaches a method of inhibiting graft versus host disease (GVHD) in a human requiring donor lymphocyte infusion (DLI) comprising contacting donor lymphocytes to be infused with an aqueous solution containing a therapeutically effective amount of L-leucyl-L-leucine methyl ester (LLME) *ex vivo*, eliminating selective cytotoxic T-cells, infusing said lymphocytes into the human, and inhibiting GVHD (see Methods and Materials, page 679, column 2 - page 680, column 1). Note that the limitation of Claim 1, "a mammal in need of DLI" is met given the teaching that the patients in the reference have received total body irradiation and would therefore die absent an infusion of donor lymphocytes, i.e., the mammal needs DLI to survive. In addition, the reference teaches that many stem cell transplantation patients suffer and die from opportunistic infections such as CMV or Aspergillus infection (see particularly Table 4). The reference also teaches that LLME treatment causes a reduction in the number of human progenitor cells (stem cells) (see particularly Abstract) and CFU-GM (see particularly page 682, column 1, paragraph 1). The reference also teaches LLME treatment at at least 1 micromolar, from about 10 to about 500 micromolar, and at least about 500 micromolar (Table 2) wherein said treatment is for at least about 15 minutes (page 680, column 1) and the freezing of treated cells (page 680, column 1).

The reference differs from the claimed invention in that it does not teach DLI after donor stem cell engraftment (Claims 2 and 3) nor the separation of $CD34^+$ and $CD34^-$ cells before the LLME treatment of the $CD34^-$ cells only (Claim 5).

Small et al. teaches donor lymphocyte infusion post-stem cell transplantation to prevent viral infections (see particularly page 468, column 2) and that the risk of

opportunistic infection in stem cell transplant patients correlates with CD4 T cells in a patient, i.e., low CD4 counts increase the risk of infection (see particularly Abstract and page 474, column 1).

The '112 patent teaches that NK cells and cytotoxic T cells are primarily responsible for GVHD after DLI (see particularly column 9, lines 17-51). The reference further teaches that *ex vivo* Leu-Leu-OMe (LLME) treatment can be used to selectively kill NK and cytotoxic T cells before DLI (see particularly column 4, lines 4-23).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to infuse LLME-treated donor lymphocytes, as taught by Rosenfeld et al., into a mammal after stem cell transplantation, in view of the combined teachings of Small et al., and the '112 patent. One of ordinary skill in the art at the time the invention was made would have been motivated to infuse LLME-treated donor lymphocytes into a mammal after stem cell transplantation because said mammals would be in need of the additional infusion to prevent viral infections, as taught by Small et al. Given the additional teaching that low CD4 T cell counts increased the risk of opportunistic infection, as taught by Small et al., and increased CD8 and NK cell counts increased the risk of GVHD, as taught by the '112 patent, one of ordinary skill in the art at the time the invention was made would have been motivated to use LLME-treated donor lymphocytes (as opposed to untreated lymphocytes) for DLI because said lymphocytes would have been increased in CD4 cells, in particular, said increase would have been achieved without the additional increase in the now depleted CD8 and NK cells, and would thus, have increased the ability to ward off opportunistic viral infection without increasing the risk of GVHD. Claim 5 is included in the rejection because it would also have been obvious in view of the combined references to separate the cells for transplantation into $CD34^+$ (stem cell) and $CD34^-$ (nonstem cell) fractions before LLME treatment, and treat only the $CD34^-$ fraction (the fraction comprising NK and cytotoxic T cells) while leaving the $CD34^+$ fraction (the fraction comprising the stem cells that differentiate into CFU-GM) untreated, thus obtaining the benefits of NK and cytotoxic T cell reduction (as set forth above) without concurrent stem cell and CFU-GM reduction.

First note that Applicant is correct in pointing out the typographical error in the previous rejection in which the '112 patent was in one instance referred to as the '756 patent.

Applicant's arguments, filed 1/28/03, have been fully considered but they are not persuasive. Applicant argues, "Applicants respectfully submit that the combination of Rosenfeld, Small, and '112 does not render claims 3 and 5 *prima facie* obvious under 35 U.S.C. § 103(a)." Applicant argues that a proper rejection must include a motivation to combine the references, an expectation of success, and that the prior art references must teach or suggest all the claim limitations. Applicant continues by arguing that "Rosenfeld, combined with Small and '112, does not teach or suggest all of the claimed elements of the present invention." Applicant continues by then arguing against the references individually.

Applicant is advised that it is the combination of the references, in light of the knowledge generally available to one of skill in the art at the time of the invention, that renders the invention of the instant claims obvious. Thus, Applicant's argument in the first paragraph of page 11 of the remarks regarding why the Rosenfeld et al. reference is deficient does not render the instant claims patentably distinct in view of the combined prior art.

Applicant argues that the Rosenfeld reference teaches treating bone marrow. Applicant is advised that bone marrow would comprise cytotoxic T lymphocytes.

Applicant argues that the references do not teach the separation of $CD34^+$ and $CD34^-$ before LLME treatment. It is the Examiner's position that said treatment would be obvious in view of the references given the teachings that LLME reduces not only cytotoxic T cells but also the number of stem cells (Rosenfeld, Abstract), thus the protection of the stem cells (by not LLME-treating them) would be an obvious advantage.

Applicant argues that Small et al. does not correct the deficiencies of Rosenfeld et al. in that "it does not teach or suggest the use of LLME to prepare T cell-depleted DLI for use in preventing GVHD following hematopoietic stem cell transplantation, nor does Small teach the separation of $CD34^+$ and $CD34^-$ cells before treatment of $CD34^-$ cells with LLME, as claimed in the present application."

Again it is the Examiner's position that the combined references, in light of the knowledge generally available to one of skill in the art at the time of the invention, renders the invention of the instant claims obvious, for the reasons of record.

Applicant argues that "In addition, '112 does not correct the deficiencies of Rosenfeld and Small," as it does not teach "treating donor lymphocytes for use after transplantation or separating $CD34^+$ cell [sic] from $CD34^-$ cells before treatment of $CD34^-$ cells with LLME, as claimed in the present application."

It is the Examiner's position that DLI after stem cell transplantation is taught by the Small et al. reference and the separation $CD34^+$ cells from $CD34^-$ cells before treatment of $CD34^-$ cells with LLME has been discussed previously.

Applicant argues "Furthermore, there would have been no motivation to combine these references, nor does the result of the purported combination teach or suggest all the elements of the claims."

It is the Examiner's position that the performance of the obviously superior method is obvious for the reasons of record and that motivation to perform said obvious method has been established.

Applicant is further advised that essentially all of the instant arguments, which generally traverse the finding that the separation $CD34^+$ cells from $CD34^-$ cells before treatment of $CD34^-$ cells with LLME would have been obvious, would only apply to the rejections of Claims 5 and 11 as only these claims comprise the limitation.

9. The following are new grounds of rejection necessitated by Applicant's amendment.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 5-11 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) The phrase, "obtaining a preparation of hematopoietic stem cells from a mammal;" in Claim 5, comprises a limitation not supported by the specification or claims as filed. The citations offered in support of the step disclose no obtaining of a preparation of HSC.

B) The phrase, "at least about one micromolar;" in Claim 7, comprises a limitation not supported by the specification or claims as filed.

C) The phrase, "from about 10 micromolar to about 500 micromolar;" in Claim 8, comprises a limitation not supported by the specification or claims as filed.

D) The phrase, "at least about 500 micromolar;" in Claim 9, comprises a limitation not supported by the specification or claims as filed.

D) The phrase, "for at least 15 minutes;" in Claim 10, comprises a limitation not supported by the specification or claims as filed.

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday and alternate Fridays from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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Primary Examiner
Technology Center 1600
March 25, 2002